IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of	) Examiner: S. Chunduru
Roland Carlsson et al.	) Art Unit: 1637
Serial No. 09/734,801	)
Filed: December 12, 2000	)
For: "A Method for in Vitro	)
Molecular Evolution of	)
Protein Function"	)

REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.111

The September 17, 2004 Official Action has been carefully reviewed. In view of the following remarks and evidence, favorable reconsideration and allowance of this application are respectfully requested.

At the outset it is noted that a shortened statutory response period of three (3) months was set forth in the September 17, 2004 Official Action. Therefore, the initial due date for response was December 17, 2004. A petition for a two (2) month extension of the response period is presented with this response, which is being filed within the two month extension period.

Applicants note with pleasure that the Examiner has withdrawn the rejections set forth in the January 27, 2004 Official Action.

At page 2 of the Official Action, the Examiner has rejected claims 1-7 under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent 6,632,610 (hereinafter the '610 patent) in view of U.S. Patent 6,337,186 (hereinafter the '186 patent).

The foregoing rejection constitutes all of the grounds set forth in the September 17, 2004 Official Action for refusing the present application.

In view of the reasons set forth in this response, Applicants respectfully submit that the 35 U.S.C. §103(a) rejection of claims 1-7, as set forth in the September 17, 2004 Official Action, cannot be maintained. This ground of rejection is, therefore, respectfully traversed.

CLAIMS 1-7 ARE NOT RENDERED OBVIOUS BY U.S. PATENT 6,632,610 IN VIEW OF U.S. PATENT 6,337,186

The Examiner has rejected claims 1-7 under 35 U.S.C. §103(a) as allegedly being unpatentable over the '610 patent in view of the '186 patent. In support of this rejection, the Examiner contends that the '610 patent teaches providing single stranded polynucleotides consisting of plus or minus strands of parent polynucleotide sequences, optionally reducing the size of the polynucleotides by fragmentation, annealing plus and minus strand populations, and amplifying the fragments which anneal to generate a polynucleotide sequence with altered characteristics. The Examiner acknowledges that '610 patent does not teach the use of an exonuclease, but contends that the '186 patent teaches the use of an exonuclease for the generation of polynucleotides of different lengths. The Examiner concludes that it would have been *prima facie* obvious to a skilled artisan to combine the teachings of the '610 patent and the '186 patent in order to arrive at the instant invention.

Applicants respectfully disagree with the Examiner's position. The instant invention relates to methods for generating a polynucleotide sequence from parent single-stranded polynucleotide sequences comprising the steps of: a) providing plus and minus strands of parent polynucleotide sequences; b) digesting the strands with an exonuclease; c) contacting the resulting fragments, whereby annealing occurs between fragments of the plus and minus strands; and d) amplifying the fragments that anneal to each other to generate

polynucleotide sequence(s) encoding protein motifs having altered characteristics as compared to the protein motifs of the parent polynucleotide.

Contrary to the Examiner's allegations, the '610 patent does **not** disclose a method for generating a polynucleotide sequence from a parent polynucleotide. Applicants submit that the '610 patent, in fact, relates to a method for the isolation and identification of polynucleotides in a sample. For example, column 8, lines 53-55 of the '610 patent state:

> The invention describes **methods for the isolation of related polynucleotides** harbouring nucleic acid differences in a polynucleotide sample." [Emphasis added.]

Examples 2-7 make it clear that the method disclosed in the '610 patent is to be used to **isolate and/or identify** polynucleotides from various sample types. For instance, Examples 3 and 6 relate to the isolation and identification of alternative splicing events for a single gene in one or several conditions. Examples 4 and 7 relate to the isolation and identification of alternative splicing isoforms of a single gene in one or more conditions. Additionally, Example 5 relates to the identification of sequence differences between the genomes of a drug-resistant and a drug-sensitive pathogen.

Thus, the '610 patent relates to an analytical method for identifying polynucleotides with altered nucleotide sequences for determining their sequence. It does not disclose a method for generating new polynucleotide sequences from a parent polynucleotide as alleged by the Examiner. There is no teaching or suggestion in the '610 patent to indicate that the disclosed method could be used to generate new polynucleotide sequences. Consequently, a person skilled in the art would not be motivated to adapt the method of the '610 patent to generate polynucleotide sequences and would

therefore not arrive at the instantly claimed subject matter.

Applicants also submit that the steps of the method disclosed by '610 patent differ from those of the instantly claimed methods. As described at columns 3-8, the method of isolation and/or identification disclosed in the '610 patent involves the steps of 1) obtaining a polynucleotide sample of containing related polynucleotides having nucleic acid differences; 2) optionally reducing the size of the polynucleotides by fragmentation; 3) annealing polynucleotides in the sample to allow the formation of heteroduplexes containing at least one internal single stranded regions (ISSRHs) between related polynucleotides; 4) selecting ISSRHs using a single-stranded trap; and 5) optionally amplifying ISSRHs selected by the single-stranded trap by polymerase chain reaction (PCR).

Applicants respectfully submit these above steps are different than the steps recited by the Examiner in the instant Official Action. In particular, the Examiner alleges, at page 3, lines 16-17 of the instant Official Action, that step 5), as numbered above, of the method disclosed in the '610 patent relates to:

> "amplifying the fragments that anneal to each other to **generate** a polynucleotide sequence **encoding altered characteristics**" [Emphasis added.]

In support of this position, the Examiner cites the passage at column 5, lines 23-25. However, a close review of this passage reveals that the ISSRHs, which are generated by the annealing of single-stranded polynucleotides, are selected and purified using a "single-stranded trap" and subsequently amplified by PCR. Notably, at column 8, lines 55-58, the "single-stranded trap" is referred to by the '610 patent as "the core of the present invention." Applicants submit, however, that the instantly claimed methods do not recite or require the isolation of any ISSRHs generated by the annealing of single-stranded polynucleotide fragments.

Applicants also submit that step 5) of the method disclosed in the '610 patent does not generate a "polynucleotide sequence encoding one or more protein motifs having altered characteristics as compared to one or more protein motifs encoded by said parent polynucleotides," as required by the instant claims. Rather, the amplification step of the '610 patent **isolates** polynucleotide sequences which have been selected from the sample by the single-stranded trap. The polynucleotides amplified by this step are therefore the same sequences that are present in the sample provided in step 1) of the method. The amplified polynucleotides may or may not encode "altered characteristics" relative to those polynucleotides present in the starting population of polynucleotides. However such sequences are not "generated" by fragmenting and annealing plus and minus polynucleotide strands, as required by the present claims. Rather, they are pre-existing variants. Applicants submit that the amplification step in the '610 patent generates copies of polynucleotides present in the sample in order to improve cloning and reduce the likelihood that the sequence of the trapped polynucleotide is altered. Indeed, at column 30 line 65 through column 31, line 6, the '610 patent teaches:

> "This optional step of amplifying the polynucleotides isolated using any method of the invention serves two purposes: i) **increasing the amount of isolated polynucleotides obtained** in order to increase the efficiency of subsequent steps such as cloning, sequence analysis or even another round of enrichment, and ii) increasing the efficiency of cloning of isolated nucleic acid differences by **avoiding eventual reparation of internal single stranded regions by recombinant bacteria**." [Emphasis added.]

Conversely, the instantly claimed methods require generation of polynucleotide sequences encoding protein motifs having altered characteristics compared to those of the parent polynucleotide - i.e., they are newly generated

polynucleotides that are not present in the starting population of polynucleotides.

As a result of this difference, the amplification step of the '610 patent is performed differently from that of the instantly claimed invention. In particular, the amplification step of the '610 patent absolutely requires the addition of oligonucleotide primers specific for internal single stranded regions (ISSRHs) of the polynucleotide selected by the single-stranded trap (see, for example, column 5, lines 23-25 and column 31, lines 11-17). If the sequence of the trapped polynucleotide is not known, the '610 patent also requires the step of ligating adaptors at the termini of the trapped polynucleotide (see, for example, columns 29-30) to serve as templates for amplification primers.

There are no such requirements in the method of the instant invention. Rather, amplification can be performed in the absence of primers and/or ligated adaptors since it is primed by the overlapping fragments that are formed by the annealing of the digested plus and minus strands of the polynucleotide sequence. There is no teaching or suggestion in the '610 patent that the amplification step could be performed without oligonucleotide primers. Accordingly, the present invention is not obvious in view of the '610 patent.

For the reasons given above, Applicants respectfully submit that the '610 patent fails to teach or suggest each and every element of the instantly claimed invention. Furthermore, Applicants submit that the present invention is not obvious over the combined disclosure of the '610 patent and the '186 patent as the combined disclosure fails to teach each and every element of the instantly claimed invention and a skilled artisan would not have been motivated to combine these two disclosures. Indeed, the Examiner cites the '186 patent for the teaching that an exonuclease may be employed for generating polynucleotide fragments. Such a teaching, however, does not make up for the shortcomings of the method

disclosed in the '610 patent as set forth above.

Furthermore, as discussed hereinabove, the '610 patent relates to an analytical method for isolating and/or identifying a polynucleotide sequence. It is therefore drawn from a technical field distinct from that of the '186 patent, which relates to a method of generating new polynucleotides by mutagenesis. Since the '610 patent does not teach or suggest the use of the disclosed method in the generation of new polynucleotide sequences, a skilled artisan apprised of this document would not have considered adapting the method of the '610 patent to generate polynucleotides. Rather, the skilled artisan would, if anything, have been more likely to adapt the methods the '186 and '601 patents in order to develop an alternative analytical method for isolating and/or identifying a polynucleotide sequence.

In light of the foregoing, Applicants submit that the rejection of claims 1-7 under 35 U.S.C. §103(a) as allegedly being unpatentable over the '610 patent in view of the '186 patent is untenable and should be withdrawn.

However, in the interest of expediting prosecution, Applicants also submit that the '610 patent is not properly citable as prior art with regard to the instant application. In support of Applicants' position, a Declaration under 37 CFR §1.131 and Exhibits A1-A21, B1-B5, and C1-C2 are provided herewith which demonstrate that the present inventors had conceived of and reduced to practice the invention claimed in the above-identified application prior to October 12, 2000, the earliest effective filing date of the '610 patent. As noted at MPEP §715.02, Applicants "may overcome a 35 U.S.C. 103 rejection based on a combination of references by showing completion of the invention by applicant prior to the effective date of any of the references." Accordingly, the instant rejection is obviated as evidenced by the Declaration and evidence submitted herewith.

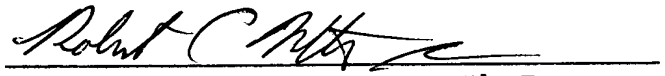
In view of the arguments set forth above and the Declaration and evidence submitted herewith, Applicants respectfully request the withdrawal of the rejection of claims 1-7 under 35 U.S.C. §103(a) as allegedly being unpatentable over the '610 patent in view of the '186 patent.

CONCLUSION

In view of the foregoing remarks and evidence, it is respectfully urged that the rejection set forth in the September 17, 2004 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number give below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
A Professional Corporation

By 
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Enclosure: Declaration by Roland Carlsson, Ann-Christin Malmborg Hager, Christina Furebring, and Carl Borrebaeck
Exhibits A1-A21
Exhibits B1-B5
Exhibits C1-C2